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CASE REPORT

Lack of $GABA_BR1$ gene variation (G1465A) in a Chinese population with temporal lobe epilepsy

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Summary GABA(B) receptor1 ($GABA_BR1$) gene is one of the susceptibility genes for temporal lobe epilepsy (TLE). Recently, it is reported that the $GABA_BR1$ polymorphism (G1465A) conferred a highly increased susceptibility to TLE. We performed a case-control study to confirm the findings. The study included a total of 112 nonlesional TLE patients and 124 controls of Chinese ancestry. Our study did not show any polymorphism in this locus, and suggested this polymorphism may not be a strong susceptibility factor for TLE among Chinese population.

Introduction

Temporal lobe epilepsy (TLE) is one of the most common epilepsy syndromes. It is often associated with hippocampal sclerosis (HS). Although the etiology of TLE remained highly controversial, growing evidence indicated that genetic predisposition appears to be an important causal factor of TLE in the last few years. GABA (γ-aminobutyric acid) is the principal inhibitory neurotransmitter in the human brain, which exerts its effects mainly through two receptor subtypes termed A and B.[1] GABA(B) receptors are highly expressed in the limbic system, specifically in CA1 and CA3 pyramidal cells of hippocampal formation, and in dentate gyrus granule cells.[2] So malfunctioning of the GABA-ergic system has been proposed as one cause for epilepsy.

Recently, Gambardella et al.[3] found a strong association between $GABA_BR1$ gene polymorphism (G1465A) and TLE in a European group. The biological significance of such a finding needs to be confirmed by independent population samples. So we performed a case-control test to research if the polymorphism was susceptibility for TLE of Chinese ancestry.

Materials and methods

Data and evaluation procedures on our patients with TLE have been reported in our previous study.[4] The

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Table 1 Clinical and epidemiologic characteristics in patients with TLE and in controls.[4]

	TLE (total = 112)		Controls (total = 124)
	HS^+ (n = 67)	HS^- (n = 45)	
Gender (F/M)	32/35	16/29	56/68
Age (years)	31.28 ± 9.84	32.13 ± 10.65	29.66 ± 7.41
Age at seizure onset (years)	16.46 ± 8.99	25.76 ± 14.25	
History of PFC, n (%)	28 (42)	7 (16)	

study consisted of 112 outpatients with nonlesional TLE who visited the Hakuai Epilepsy Center in Peking Union Medical College Hospital from December 2000 to July 2001. Informed consent was obtained from all subjects. Diagnosis of nonlesional TLE was based on comprehensive clinical, neuropsychological, EEG, and MR evaluations. According to the findings of MRI, patients were divided into two groups: 67 TLE patients with hippocampal sclerosis (HS) (TLE-HS^+) and 45 patients without HS (TLE-HS^-). The main clinical and epidemiologic data are summarized in Table 1. One hundred and twenty-four unrelated neurologically normal subjects, matched for age, sex, ethnicity, were also randomly selected as controls. Both the patients and the controls were of Chinese ancestry and came from the northern regions of China.

Venous blood was drawn from each individual, and genomic DNA was prepared from whole blood by using a standard proteinase K digestion and phenol-chloroform method. A 441-bp fragment in position of $GABA_BR1$ exon 7 was amplified by polymerase chain reaction (PCR). Primer pairs and the conditions for the PCR were previously described.[3,5] The PCR products were digested with restriction enzyme EagI (the G to A transition destroys an EagI restriction site, the 441-bp amplification fragment cannot be digested into 258- and 183-bp fragments in individuals carrying such a DNA change), run on a 12% polyacrylamide gel, and viewed and photographed under ultraviolet light after staining with ethidium bromide.

Results

In contrast with the previous study in Europe, our study did not show any polymorphism in this locus, only genotype G/G was observed in all patients and controls.

Discussion

In 1998, the gene encoding $GABA_BR1$ was cloned, several polymorphisms of human $GABA_BR1$ gene have been identified, but only two were missense mutations.[5] The missense mutation (G1465A) led to an amino acid substitution Gly489Ser within the N-terminal extracellular domain of the GABA(B) receptor, which was necessary for heteromeric assembly of such a receptor and, therefore, might affect its ligand binding properties. Gambardella et al. showed the $GABA_BR1$ gene polymorphism (G1465A) conferred a highly increased susceptibility to TLE. The A/G genotype was found in 17% of the 141 patients with TLE and in only 0.5% of the 372 controls ($p < 0.0001$).[3] The authors also found that patients carrying the A allele had a significantly higher risk ($p = 0.003$, OR = 6.47, 95% CI = 2.02–20.76) of developing drug-resistant TLE. Furthermore, the age at onset of seizures tended to be lower in patients with A/G genotype, but the difference was not significant.

In the last few years, significant association with sporadic TLE have been reported in IL-1b,[6] APOE,[7] PDYN,[8] and PRNP.[9] Otherwise, results from follow-up studies were conflicted. This study also failed to document any association between $GABA_BR1$ (G1465A) variation and TLE, only genotype G/G was observed in all patients and controls.

Failure to replicate a genetic association study could be caused by several factors, and they have been discussed extensively in previous studies.[10] Patients in the present study and the previous study all met the inclusion criteria for nonlesional TLE. The sample sizes were also similar (112 in our study and 141 in the original report). We must keep in mind that common diseases arise from interaction of several genes, with additional environmental influences, and are much more complex, which can lead to the discrepancy between independent populations in gene-disease associations. In addition, rare susceptibility alleles may be ethno-geographically localized, and dissimilar disease-causing alleles may predominate in different populations, which may also result in nonreplication.

Though further studies in independent population samples are needed to determine whether the GABABR1 (G1465A) variation is a susceptibility factor for TLE, our results suggest that this mutation may not be a strong susceptibility factor for TLE.

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